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The Mechanism of Vesicle Fusion as Revealed by Molecular Dynamics Simulations - SUPPORTING INFORMATION

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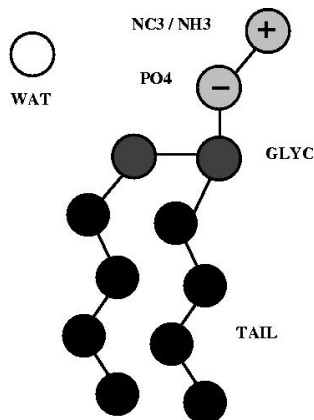


Figure 1: Structure and nomenclature of the molecules in the coarse grained model

0.1 The Coarse Grained Model

In our coarse grained model DPPC and DPPE are represented by twelve coarse grained atoms, as shown in figure 1. The headgroup consists of two hydrophilic groups ("NC3" for the choline group of PC or "NH3" for the amine group of PE, and "PO4" for the phosphate moiety) and two intermediately hydrophilic ones for the glycerol moiety ("GLYC"). Each of the two tails is modelled by four hydrophobic particles (type "TAIL"). The oleoyl tail of POPE is represented by five rather than four of such particles. LysoPC is simply obtained by removing one of the tails of DPPC. The solvent is modeled by individual hydrophilic particles ("WAT") each representing four real water molecules. The coarse grained atoms interact in a pairwise manner via a Lennard-Jones (LJ) potential. Five different LJ potentials are used, ranging from weak (labelled "repulsive", mimicking hydrophobic interactions) to strong (labelled "attractive", for hydrophilic interactions) with three levels in between. The five different interaction strengths are obtained by changing the well depth ϵ only. All CG particles have exactly the same size of $\sigma = 0.47$ nm, and the same mass of 72 amu (corresponding to four water molecules). The LJ parameters used in the simulations are summarized in table 1.

In addition to the LJ interactions, a screened Coulomb interaction (with $\epsilon_r = 20$) is used to model the electrostatic interaction between the zwitterionic headgroups. The NC3 and the NH3 group both bear a charge of +1, and the phosphate group bears a charge of -1. Both LJ and Coulomb interactions are only short ranged, however, using a shift based cutoff of 1.2 nm. Soft springs between bonded pairs keep the molecule together. The spring constant $K_{bond} = 1250$ kJ mol⁻¹ nm⁻² with an equilibrium distance of σ . Angle potentials provide the appropriate stiffness for the lipid molecule. A cosine based angle potential is used with a weak force constant $K_{angle} = 25$ kJ mol⁻¹ rad⁻² and an equilibrium angle of 180°. This angle potential is used for the triplets GLYC-C1-C2, C1-C2-C3, and C2-C3-C4 for both tails and for PO4-GLYC-C1. An additional angle potential with an equilibrium angle of 120° is furthermore

Table 1: Interaction Matrix: Level of interaction I (attractive, $\epsilon=5$ kJ/mol), II (semi-attractive, $\epsilon=4.2$ kJ/mol), III (intermediate, $\epsilon=3.4$ kJ/mol), IV (semi-repulsive, $\epsilon=2.6$ kJ/mol) or V (repulsive, $\epsilon=1.8$ kJ/mol).

Group	WAT	NC3/PO4	NH3	GLYC	TAIL
WAT	I	I	I	III	V
NC3/PO4	I	III	I	III	V
NH3	I	I	II	II	V
GLYC	III	III	II	II	IV
TAIL	V	V	V	IV	III

used for the glycerol backbone PO4-GLYC-GLYC. To model the double bond of the oleoyl tail of POPE, the equilibrium angle of C2-C3-C4 is set to 110° with a somewhat larger force constant $K_{angle} = 55 \text{ kJ mol}^{-1} \text{ rad}^{-2}$.

The setup of our CG forcefield is comparable to the recently developed CG lipid forcefields of Goetz *et al.* [1] and Shelley *et al.* [2], which are based on the pioneering work of Smit *et al.* [3]. The current version of our CG forcefield represents the lamellar state of many lipids including DPPC and DPPE very well. The area per lipid for DPPC at 323 K is 0.65 nm^2 (experimental 0.64 nm^2 [4]) and for DPPE 0.62 nm^2 at 342 K (experimental 0.605 nm^2 [5]). The thickness of the CG bilayer, measured from the peaks of the phosphate distribution, measures $4.0 \pm 0.1 \text{ nm}$, close to the experimentally determined bilayer thickness of 3.85 nm for the lamellar phase of DPPC in the liquid-crystalline phase [4]. The electron density distributions along the bilayer normal are very close to those obtained with atomistic simulations [6].

Because the potential functions of the CG model are smoother compared to atomistic models, the dynamics of CG systems is significantly faster. On the one hand this is advantageous for it allows faster sampling of the configurational space, on the other hand it makes the interpretation of the timescale somewhat arbitrary. Based on a comparison of diffusion rates of real water and the CG water, the CG model is found to diffuse four times faster. Fortunately, similar factors are found not only for bulk alkane systems, but also for lipid systems. The relative dynamics in the CG model therefore seems well preserved. In order to obtain a physically meaningful timescale, the timescale used to present the results is an effective time, i.e. the actual simulation time multiplied by a factor of four. With this effective timescale, both the diffusion rate of water molecules ($2 \cdot 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ at 300K) and the lateral diffusion rates of lipids ($3 \cdot 10^{-7} \text{ cm}^2 \text{ s}^{-1}$ for DPPC at 323K) are close to the experimental estimates. Also the timescales of self-aggregation of lipids into bilayers are well reproduced (if compared to atomistic simulations). Details concerning the development of the CG forcefield including a more extensive comparison between CG bilayers and atomistic bilayers will be published elsewhere. The parameters and topologies can also be obtained from our web-site (<http://md.chem.rug.nl/marrink/coarsegrain.html>).

0.2 Cross Sections Through Stalk Region

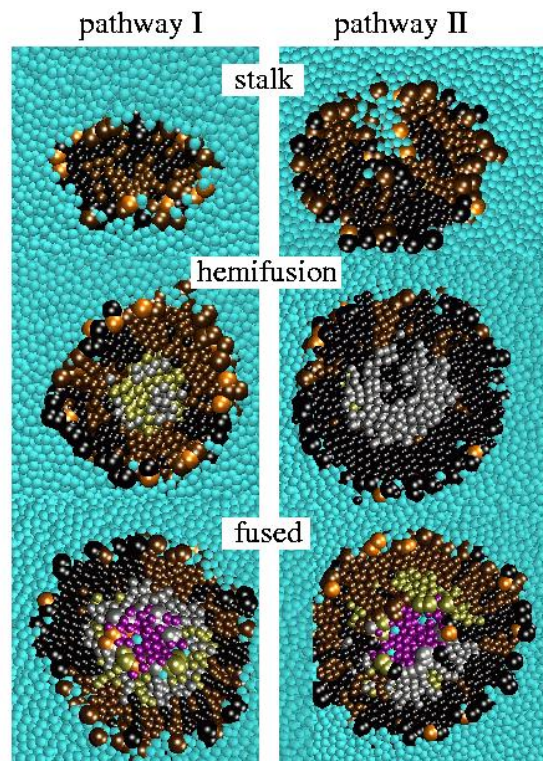


Figure 2: Comparison of the transition from stalk to opening of the fusion pore in both pathways observed for the fusion of mixed DPPC/DPPE vesicles. Slabs perpendicular to the fusion axis are shown, cutting through the stalk or hemifusion diaphragm. Lipid headgroups are represented by large spheres. Different colors distinguish between lipids in the inner (yellow/silver) and outer monolayer (brown/black) and between the two vesicles (brown and yellow vs black and silver). Orange spheres denote the ethanolamine site of PE, blue spheres denote exterior water, purple spheres interior water. Note the differences in stalk structure (bent in pathway II) and in the composition of the HD (mixed in pathway I, almost entirely from a single vesicle in pathway II).

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